IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re New Divisional U.S. Patent Application of:			
Applicant:	**CHANG, Kwen-Jen, et al.**	**Docket No.:**	**4080-109 CIP DIV 2**
Application No.:	**Not Assigned**	**Examiner:**	**Not Assigned**
Prior App. No.:	**09/352,308**	**Group Art Unit:**	**Not Assigned**
Date Filed:	**October 9, 2001**		
Title:	**COMPOSITIONS AND METHODS FOR REDUCING RESPIRATORY DEPRESSION AND ATTENDANT SIDE EFFECTS OF MU OPIOID COMPOUNDS**		

EXPRESS MAIL CERTIFICATE

I hereby certify that I am mailing the attached documents to the Commissioner for Patents on the date specified, in an envelope addressed to the Commissioner for Patents, Washington, D.C., 20231 and Express Mailed under the provisions of 37 CFR 1.10.

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October 9, 2001
Date

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PRELIMINARY AMENDMENT

Commissioner for Patents
Box Patent Application
Washington, DC 20231

Sir:

Preliminary to examination of this application, please amend the application as follows:

In the Specification

1. On page 1, please replace the paragraph beginning at line 31, with the following paragraph:

This is a divisional application of United States patent application no. 09/352,308 filed July 12, 1999 and issued October 9, 2001 as U.S. Patent 6,300,332, which claims priority to United States patent application 08/887,312 filed July 3, 1997, which is a continuation-in-part of United States patent application no. 08/658,726, filed June 5, 1996. The disclosures of the following applications are hereby incorporated herein by reference in their entirety: United States patent application no. 08/658,726 filed June 5, 1996; United States patent application no. 08/169,879 filed December 17, 1993; United States patent application no. 08/098,333 filed July 30, 1993; United States patent application no. 08/430,677 filed April 28, 1995; International Patent Application no. PCT/GB93/00216 filed February 2, 1993; Great Britain patent application 9202238.3 filed 3 February 1992; and all applications from which they claim priority, or from which priority is claimed.

Amend the claims as follows:

Cancel claims 1-46 in the original application.

Add new claims 47-75, as follows:

47. A pharmaceutical composition comprising:

(1) an effective amount of a bioactive compound mediating respiratory depression, muscle rigidity, and/or nausea/vomiting as an unwanted side effect thereof; and

(2) a non-polypeptide δ receptor activating agent effective for combating said side effect.

48. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises a diarylmethylpiperazine or a diarylmethylpiperazine compound.

49. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises a diarylmethylpiperazine compound.

50. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises 3290W93.

51. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises BW373U86.

52. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises an agent selected from the group consisting of:

I. diarylmethylpiperazine compounds;

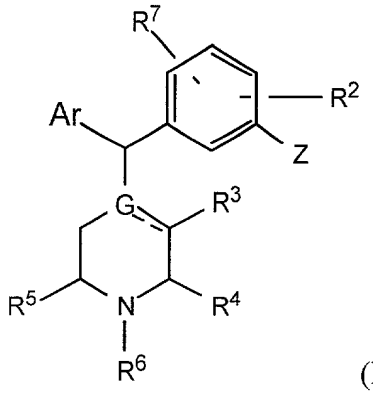
II. diarylmethylpiperidine compounds;

III. deltorphin I; and

III. deltorphin II.

53. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises an agent selected from the group consisting of:

I. δ agonist compounds of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent R^1;

Y is selected from the group consisting of:

hydrogen;

halogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_1-C_6 haloalkyl;

C_1-C_6 alkoxy;

C_3-C_6 cycloalkoxy;

sulfides of the formula SR^8 where R^8 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, arylalkyl having a C_5-C_{10} aryl moiety and an C_1-C_6 alkyl moiety, or C_5-C_{10} aryl;

sulfoxides of the formula SOR^8 where R^8 is the same as above;

sulfones of the formula SO_2R^8 where R^8 is the same as above;

nitrile;

C_1-C_6 acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where R^8 is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 hydroxyalkyl, C_2-C_6 methoxyalkyl, C_3-C_6 cycloalkyl, or C_5-C_{10} aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where R^9 and R^{10} are the same as above, or C_2-C_{30} peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where R^9 and R^{10} are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

R^1 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^2 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^3, R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3, R^4 or R^5 is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R^3, R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms;

R^6 is selected from the group consisting of:

hydrogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_3-C_6 cycloalkyl;

arylalkyl having C_5-C_{10} aryl and C_1-C_6 alkyl moieties;

alkoxyalkyl having C_1-C_4 alkoxy and C_1-C_4 alkyl moieties;

C_2-C_4 cyanoalkyl;

C_2-C_4 hydroxyalkyl;

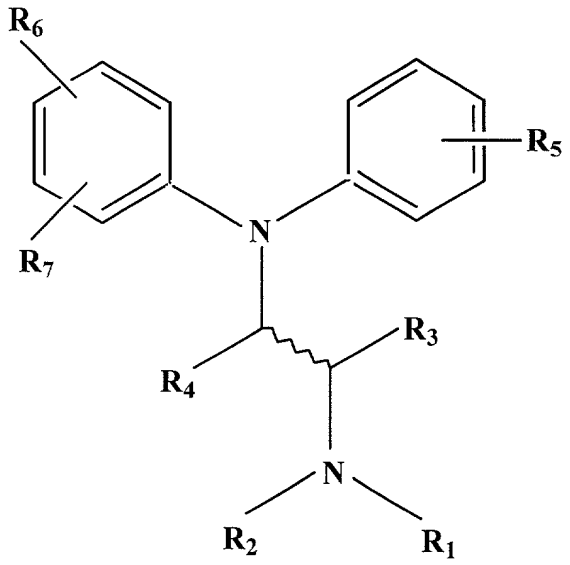
aminocarbonylalkyl having a C_1-C_4 alkyl moiety; and

$R^{12}COR^{13}$, where R^{12} is C_1-C_4 alkylene, and R^{13} is C_1-C_4 alkyl or C_1-C_4 alkoxy; and

R^7 is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof;

II. delta agonist compounds of the formula:



in which,

R_1 and R_2, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, C_{3-5} alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by oxygen.

R_3 and R_4, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, or R_4 is oxygen forming with the carbon atom to which is attached a C=O group;

R_5 is hydrogen, hydroxy, C_{1-3} alkoxy, thiol or alkylthio;

R_6 is phenyl, halogen, NH_2 or a para or meta -C(Z)-R_8 group, in which Z is oxygen or sulphur;

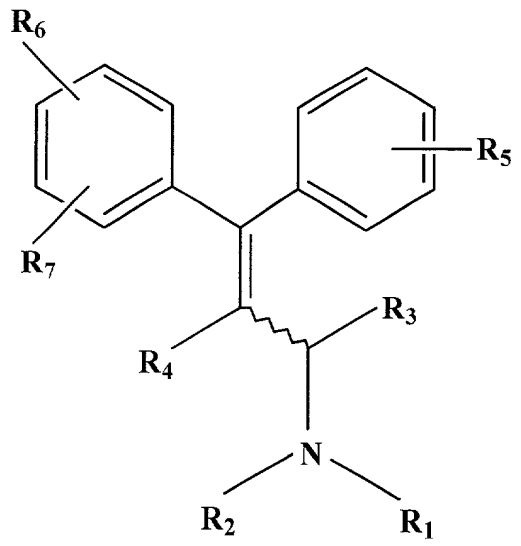
R_8 is C_{1-8}-alkyl, C_{1-8}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl or aralkyl,

or R_6 is a para or metal -N-C(Z)-R_{12} group, where R_{11} is attached to the N.

in which R_{11} and R_{12} which may the same or different are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring, and Z is as defined above; and,

R_7 is hydrogen, straight or branched C_{1-8} alkyl or halogen; and

III. delta agonist compounds of the formula:



in which,

R_1 and R_2, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, C_{3-5} alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by oxygen.

R_3 and R_4, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl;

R_5 is hydroxy, C_{1-6} alkoxy, thiol or alkylthio;

R_6 is a -C(Z)-Rg group, in which Z is oxygen or sulphur, R_8 is C_{1-8}-alkyl, C_{1-8}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl or aralkyl,

or R_6 is a $-N-C(Z)-R_{12}$ group (with R_{11} on the nitrogen)

in which R_{11} and R_{12} have the same meaning as R_9 and R_{10} or together form an optionally substituted heterocyclic ring and Z is as defined above, and R_7 is hydrogen, straight or branched C_{1-8} alkyl or halogen.

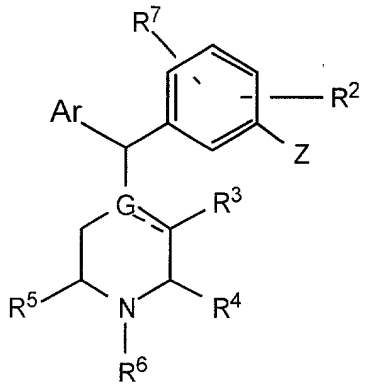
54. The pharmaceutical composition of claim 47, in a form suitable for injectable or spinal administration.

55. A pharmaceutical composition comprising:

(a) an effective amount of a bioactive compound mediating respiratory depression; and

(b) an effective amount of a non-polypeptide δ receptor activating agent effective for combating said respiratory depression.

56. A pharmaceutical composition comprising an effective amount of a bioactive composition mediating respiratory depression, and an effective amount of a compound for reducing, treating or preventing respiratory depression, of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent R^1;

Y is selected from the group consisting of:

hydrogen;

halogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_1-C_6 haloalkyl;

C_1-C_6 alkoxy;

C_3-C_6 cycloalkoxy;

sulfides of the formula SR^8 where R^8 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, arylalkyl having a C_5-C_{10} aryl moiety and an C_1-C_6 alkyl moiety, or C_5-C_{10} aryl;

sulfoxides of the formula SOR^8 where R^8 is the same as above;

sulfones of the formula SO_2R^8 where R^8 is the same as above;

nitrile;

C_1-C_6 acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where R^8 is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 hydroxyalkyl, C_2-C_6 methoxyalkyl, C_3-C_6 cycloalkyl, or C_5-C_{10} aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where R^9 and R^{10} are the same as above, or C_2-C_{30} peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where R^9 and R^{10} are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

R^1 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^2 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^3, R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3, R^4 or R^5 is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R^3, R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms;

R^6 is selected from the group consisting of:

hydrogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_3-C_6 cycloalkyl;

arylalkyl having C_5-C_{10} aryl and C_1-C_6 alkyl moieties;

alkoxyalkyl having C_1-C_4 alkoxy and C_1-C_4 alkyl moieties;

C_2-C_4 cyanoalkyl;

C_2-C_4 hydroxyalkyl;

aminocarbonylalkyl having a C_1-C_4 alkyl moiety; and

$R^{12}COR^{13}$, where R^{12} is C_1-C_4 alkylene, and R^{13} is C_1-C_4 alkyl or C_1-C_4 alkoxy; and

R^7 is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof.

57. The pharmaceutical composition according to claim 56, wherein Ar is a 6-member carbocyclic aromatic (benzene) ring and R^1 is hydrogen.

58. The pharmaceutical composition according to claim 56, wherein Y is a carboxamide of the formula $CONR^9R^{10}$.

59. The pharmaceutical composition according to claim 56, wherein R^9 and R^{10} together form a ring of five or six atoms, thereby forming a pyrrolidinyl or piperidino ring.

60. The pharmaceutical composition according to claim 56, wherein R^9 and R^{10} are the same or different and are each independently selected from hydrogen, C_1 alkyl and C_2 alkyl.

61. The pharmaceutical composition according to claim 56, wherein Y is hydrogen.

62. The pharmaceutical composition according to claim 56, wherein Y is a sulfone of the formula SO_2R^8 and R^8 is C_1-C_6 alkyl.

63. The pharmaceutical composition according to claim 56, wherein G is N, R^7 and R^2 are each hydrogen, and Z is hydroxyl.

64. The pharmaceutical composition according to claim 56, wherein R^6 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl.

65. The pharmaceutical composition according to claim 56, wherein R^3, R^4 and R^5 are hydrogen or methyl, where the total number of methyl groups is one or two.

66. The pharmaceutical composition according to claim 56, wherein R^3 and R^5 are both methyl, and R^4 is hydrogen.

67. The pharmaceutical composition according to claim 47, wherein the δ receptor activating agent comprises a compound selected from the group consisting of:

(-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

(-)-4-((αR)-α-((2R,5R)-2,5-dimethyl-4-propyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

4-((αR)-α-(2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

N,N-diethyl-4-((αR)-3-hydroxy-α-((2R,5R)-2,5-dimethyl-1-piperazinyl)benzyl)benzamide;

4-((αR)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-methyl-benzamide;

3-((αR)- α-((2S, 5S)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-N,N-diethyl-4-((αR*)-3-hydroxy-α-((2R*,5S*)-2,4,5-trimethyl-1-piperazinyl)benzyl)-benzamide;

(+)-4-((αS)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

3-((αR)-4-(piperidinocarbonyl)- α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

3-((αR)-4-(1-pyrrolidinylcarbonyl)-α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

(±)-3-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-4-(methylsulfonyl)benzyl)-phenol;

(±)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(+)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfon-amide; or

(-)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-4-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxbenzyl)benzamide;

(±)-4-((αR*)-α-((2R*,5S*)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

(±)-cis-4-(α-(4-allyl-3,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

cis-4-(α-(3,5-dimethyl-4-(methylallyl)-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

and pharmaceutically acceptable salts thereof.

68. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises

(-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide or a pharmaceutically acceptable salt thereof.

69. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises an opiate compound.

70. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises an opiate analgesic compound.

71. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises a μ opiate compound.

72. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises at least one active ingredient selected from the group consisting of alcohol, aldesleukin, alfentanil, bremazocine, buprenorphine, butorphanol, chloropromazine, clozapine, codeine, dantrolene, diazepam, dihydrocodeine, etorphine, fentanyl, flurazepam, heroin, hydrocodone, hydromorphone, ketamine, larazepam, levallorphen, levorphanol, meperidine, methadone, methohexital, mitomycin, morphine, nalbuphine, opium, oxazepam, oxycodone, oxymorphone, pentazocine, phenobarbital, porfimer, propoxyphene, resperidone, sufentanil, temazepam, thiopental, thiorzadine, tramadol, trimethaphan, and zolpidem.

73. A pharmaceutical composition comprising:

(1) an effective amount of a bioactive compound mediating respiratory depression, muscle rigidity, and/or nausea/vomiting as an unwanted side effect thereof, with the proviso that said bioactive compound is not morphine; and

(2) a delta receptor agonist.

74. A pharmaceutical composition comprising:

(1) an effective amount of a bioactive compound mediating an unwanted side effect thereof; and

(3) a non-polypeptide δ receptor activating agent effective for combating said side effect.

75. The pharmaceutical composition of claim 74, wherein the δ receptor activating agent comprises a diarylmethylpiperazine or a diarylmethylpiperazine compound.

REMARKS

Enclosed is a true and exact copy of the prior copending application No. 09/352,308. The claims 1-46 have been cancelled and new claims 47-75 have been added herein.

The fees for this application have been calculated based on the number of claims in the application after the entry of this amendment. Please charge any deficiency and credit any excess to deposit account 08-3284 of Intellectual Property/Technology Law.

Respectfully submitted,

Steven J. Hultquist
Registration No. 28,021

INTELLECTUAL PROPERTY/ TECHNOLOGY LAW
Research Triangle Park, NC 27709
Phone: (919) 419-9350
Fax: (919) 419-9354
Attorney File: 4080-109 CIP DIV2

APPENDIX A

Version with Markings to Show Changes Made

1. On page 1, the paragraph beginning at line 31 has been changed, as follows:

This is a divisional application of United States patent application no. 09/352,308 filed July 12, 1999 and issued October 9, 2001 as U.S. Patent 6,300,332, which claims priority to United States patent application 08/887,312 filed July 3, 1997, which is a continuation-in-part of United States patent application no. 08/658,726, filed June 5, 1996. The disclosures of the following applications are hereby incorporated herein by reference in their entirety: United States patent application no. 08/658,726 filed June 5, 1996; United States patent application no. 08/169,879 filed December 17, 1993; United States patent application no. 08/098,333 filed July 30, 1993; United States patent application no. 08/430,677 filed April 28, 1995; International Patent Application no. PCT/GB93/00216 filed February 2, 1993; Great Britain patent application 9202238.3 filed 3 February 1992; and all applications from which they claim priority, or from which priority is claimed.